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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No. 0053330

MEMORANDUM

DATE: June 9, 2005

SUBJECT: **Resmethrin:** Quantitative Risk Assessment (Q_1^*) Based On Swiss Crl:CD-1(ICR)BR Mouse and Crl:CD BR Rat Dietary Studies With $^3/_4$'s Interspecies Scaling Factor

P.C. Code: 097801

TO: William Dykstra, Toxicologist
Reregistration Branch 4
Health Effects Division (7509C)

FROM: Lori L. Brunsman, Statistician
Science Information Management Branch
Health Effects Division (7509C)

THROUGH: Jess Rowland, Branch Chief
Science Information Management Branch
Health Effects Division (7509C)

Summary

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Resmethrin based upon male mouse liver combined adenoma and/or carcinoma tumor rates is 5.621×10^{-2} in human equivalents. The dose levels used from the 105-week dietary study were 0, 300, 600 and 1200 ppm of Resmethrin. The corresponding uncensored tumor rates for the male mouse liver combined tumors were 11/100, 10/50, 14/50 and 18/50, respectively.

Background

On April13, 2005, the Carcinogenicity Assessment Review Committee recommended that a low dose extrapolation model be applied to the experimental animal tumor data and that

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quantifications of risk be estimated for male mouse liver and female rat liver and uterine tumors for Resmethrin. The most potent unit risk will be used for the purpose of lifetime cancer risk assessment by the Agency. In this case, the most potent unit risk, Q_1^*, is that for male mouse liver adenoma and/or carcinoma combined tumor rates at 5.621×10^{-2} in human equivalents.

For the conversion to human equivalents, weights of 0.35 kg for the rat, 0.03 kg for the mouse, 70 kg for humans, molecular weight of 338.4456, and life-span defaults of 105 weeks for both the male mice and female rats. The unit risks, Q_1^{*s}, for male mice and female rats were obtained by the application of the time-to-tumor Weibull model, which uses uncensored tumor rates. All unit risks have been converted from animals to humans by use of the $^3/_4$'s scaling factor (QRisk, STATOX for Windows program, Version 4.5, Environ International Corporation, 2005)[1].

It is to be noted that the Q_1^* $(mg/kg/day)^{-1}$ is an estimate of the upper bound on risk and that, as stated in the EPA Risk Assessment Guidelines, "the true value of the risk is unknown, and may be as low as zero."

Mouse Dose-Response Analysis

A carcinogenicity study in Swiss Crl:CD-1(ICR)BR mice was conducted by Bio-Research Laboratories, Ltd., Senneville, Quebec, Canada, for Roussel UCLAF Corporation, Montvale, New Jersey, and dated January 8, 1992 (Study No. 83754, MRID No. 43052101).

Male mice showed a significant increasing trend in mortality, at $p < 0.01$, with increasing doses of Resmethrin, as well as significant differences in the pair-wise comparisons of the 600 and 1200 ppm dose groups with the controls, both at $p < 0.05$ (**Resmethrin:** Qualitative Risk Assessment Based On Crl:CD BR Rat and Swiss Crl:CD-1(ICR)BR Mouse Dietary Studies, L. Brunsman, 4/12/2005, TXR No. 0053189).

Male mice had a significant increasing trend, and a significant difference in the pair-wise comparison of the 1200 ppm dose group with the controls, for liver adenomas and/or carcinomas combined, both at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 600 ppm dose group with the controls at $p < 0.01$ and of the 300 ppm dose group with the controls at $p < 0.05$, both for liver adenomas and/or carcinomas combined.

Additional Q_1^* Calculations

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Resmethrin based upon female rat liver adenoma and/or

[1]See memo - Deriving Q_1^*s Using the Unified Interspecies Scaling Factor, P.A. Fenner-Crisp, Director, HED, 7/1/94.

carcinoma combined tumor rates is 4.502×10^{-3} in human equivalents. The dose levels used from the 105-week dietary study were 0, 250, 1000 and 2500 ppm of Resmethrin. The uncensored tumor rates were 1/65, 0/65, 1/65 and 14/65, respectively.

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Resmethrin based upon female rat uterine endometrial stromal polyp rates is 7.673×10^{-3} in human equivalents. The dose levels used from the 105-week dietary study were 0, 250, 1000 and 2500 ppm of Resmethrin. The uncensored tumor rates were 0/65, 1/65, 3/65 and 5/65, respectively.

date: 06/08/2005 at time: 15:51
Risk Assessment : 662
Chemical : RESMETHRIN
Sex : Male
Lesions:
Liver : Adenoma
Liver : Carcinoma

	Experimental	Target
Species:	MOUSE	Human
Body Weight:	0.03000 kg	70.00 kg
Lifespan:	105 weeks	70 years
Breathing Rate:	0.34700E-01 l/min	0.83300 m^3/hr
Food Consumption:	3.90 g/day	1400.00 g/day
Drinking Rate:	6.00 ml/day	2.0 L/day

Route: Food (ppm)
Dosing: Hrs/Day : 24.0
Days/Week : 7.0
Weeks : 105.0
Weeks of Study : 105.0
Animal to Human Conversion Method: Body Weight ^ 3/4
Conver. Factor 1 (from route units to mg/kg/day) 0.13000
Conver. Factor 2 (from mg/kg/day to a-to-h units) 0.41618
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.34572

Overall Conversion Factor = 1.87046E-02
Model: Time-to-Tumor Weibull
p(d) = 1 - exp((-q0 - q1 * d - q2 * d^2 - q3 * d^3) * (t - t0)^c)
Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (ppm)	Human Equivalent per (mg/kg/day)
q(0) =	9.082517855352E-10	4.795501089929E-09
q(1) =	3.618396887829E-12	1.021397424223E-09
q(2) =	0.00000000000	0.00000000000
q(3) =	0.00000000000	0.00000000000
c =	4.10371155044	4.10371155044
t0 =	0.00000000000 (weeks)	0.00000000000 (years)

Maximum Log-likelihood -106.045190091

Group	Untransformed Dose (ppm)	Human Dose (mg/kg/day)	#Incidental Responses Observed	#Fatal Responses Observed	#Animals
1	0.00000	0.00000	11	0	100
2	300.000	5.61139	10	0	50
3	600.000	11.2228	14	0	50
4	1200.00	22.4456	18	0	50

Calculations are based on Extra Risk
Risk calculations at time 105.0 wks (animal) equiv. to 70 yrs (Human)
Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)
Lower Bound = 8.78473E-03 MLE= 3.81017E-02 Upper Bound (q1*)= 5.62092E-02

Extra Risk	Time (yrs)	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10	70	1.8744	2.7652	6.3397
0.05	70	0.91254	1.3462	3.7702
0.01	70	0.17880	0.26378	0.99883
0.005	70	8.91765E-02	0.13156	0.53092
0.001	70	1.77996E-02	2.62586E-02	0.11265
0.0001	70	1.77916E-03	2.62468E-03	1.14315E-02
1.000E-5	70	1.77908E-04	2.62456E-04	1.14781E-03
1.000E-6	70	1.77907E-05	2.62455E-05	1.13834E-04

date: 06/08/2005 at time: 15:10
Risk Assessment : 661
Chemical : RESMETHRIN
Sex : Female
Lesions:
Liver : Adenoma
Liver : Carcinoma

	Experimental	Target
Species:	RAT	Human
Body Weight:	0.35000 kg	70.00 kg
Lifespan:	105 weeks	70 years
Breathing Rate:	0.18050 l/min.	0.83300 m^3/hr
Food Consumption:	17.50 g/day	1400.00 g/day
Drinking Rate:	35.00 ml/day	2.0 L/day

Route: Food (ppm)
Dosing: Hrs/Day : 24.0
Days/Week : 7.0
Weeks : 105.0
Weeks of Study : 105.0
Animal to Human Conversion Method: Body Weight ^ 3/4
Conver. Factor 1 (from route units to mg/kg/day) 5.00000E-02
Conver. Factor 2 (from mg/kg/day to a-to-h units) 0.76916
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.34572
Overall Conversion Factor = 1.32957E-02
Model: Time-to-Tumor Weibull
p(d) = 1 - exp(-q0 - q1 * d - q2 * d^2 - q3 * d^3) * (t - t0)^c)
Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (ppm)	Human Equivalent per (mg/kg/day)
q(0) =	3.127168223873E-14	3.189968751236E-13
q(1) =	0.00000000000	0.00000000000
q(2) =	0.00000000000	0.00000000000
q(3) =	6.688962170637E-23	2.903062233427E-16
c =	5.72791170735	5.72791170735
t0 =	0.00000000000 (weeks)	0.00000000000 (years)

Maximum Log-likelihood -40.7704131760

Group	Untransformed Dose (ppm)	Human Dose (mg/kg/day)	#Incidental Responses Observed	#Fatal Responses Observed	#Animals
1	0.00000	0.00000	1	0	65
2	250.000	3.32394	0	0	65
3	1000.00	13.2957	1	0	65
4	2500.00	33.2394	14	0	65

Calculations are based on Extra Risk
Risk calculations at time 105.0 wks (animal) equiv. to 70 yrs (Human)
Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)
Lower Bound = 1.42959E-06 MLE= 2.20701E-06 Upper Bound (q1*)= 4.50199E-03

Extra Risk	Time (yrs)	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10	70	15.096	21.400	33.038
0.05	70	9.8908	16.835	25.990
0.01	70	2.2160	9.7781	15.096
0.005	70	1.1113	7.7544	11.971
0.001	70	0.22222	4.5318	6.9962
0.0001	70	2.22135E-02	2.1031	3.2469
1.000E-5	70	2.22125E-03	0.97618	1.5071
1.000E-6	70	2.22124E-04	0.45310	0.69950

date: 06/09/2005 at time: 14:28
Risk Assessment : 661
Chemical : RESMETHRIN
Sex : Female
Lesions:
Uterus : Endometial Stromal Polyp

	Experimental	Target
Species:	RAT	Human
Body Weight:	0.35000 kg	70.00 kg
Lifespan:	105 weeks	70 years
Breathing Rate:	0.18050 l/min	0.83300 m^3/hr
Food Consumption:	17.50 g/day	1400.00 g/day
Drinking Rate:	35.00 ml/day	2.0 L/day

Route: Food (ppm)
Dosing: Hrs/Day : 24.0
Days/Week : 7.0
Weeks : 105.0
Weeks of Study : 105.0
Animal to Human Conversion Method: Body Weight ^ 3/4
Conver. Factor 1 (from route units to mg/kg/day) 5.00000E-02
Conver. Factor 2 (from mg/kg/day to a-to-h units) 0.76916
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.34572

Overall Conversion Factor = 1.32957E-02
Model: Time-to-Tumor Weibull
p(d) = 1 - exp((-q0 - q1 * d - q2 * d^2 - q3 * d^3) * (t - t0)^c)
Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (ppm)	Human Equivalent per (mg/kg/day)
q(0) =	0.00000000000	0.00000000000
q(1) =	7.949042242169E-12	2.363863502732E-09
q(2) =	0.00000000000	0.00000000000
q(3) =	0.00000000000	0.00000000000
c =	3.39040177068	3.39040177068
t0 =	0.00000000000 (weeks)	0.00000000000 (years)

Maximum Log-likelihood -34.0419231846

Group	Untransformed Dose (ppm)	Human Dose (mg/kg/day)	#Incidental Responses Observed	#Fatal Responses Observed	#Animals
1	0.00000	0.00000	0	0	65
2	250.000	3.32394	1	0	65
3	1000.00	13.2957	3	0	65
4	2500.00	33.2394	5	0	65

Calculations are based on Extra Risk
Risk calculations at time 105.0 wks (animal) equiv. to 70 yrs (Human)
Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)
Lower Bound = 8.18138E-06 MLE= 4.25839E-03 Upper Bound (q1*)= 7.67310E-03

Extra Risk	Time (yrs)	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10	70	13.731	24.742	63.840
0.05	70	6.6848	12.045	31.080
0.01	70	1.3098	2.3601	11.638
0.005	70	0.65326	1.1771	8.3175
0.001	70	0.13039	0.23495	3.7922
0.0001	70	1.30332E-02	2.34842E-02	1.2150
1.000E-5	70	1.30326E-03	2.34831E-03	0.38594
1.000E-6	70	1.30325E-04	2.34830E-04	0.12223

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